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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/600,027	09/06/00	TANABE K	2000_0973A

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EXAMINER	
KATCHERES,K	
ART UNIT	**PAPER NUMBER**
1636	10

DATE MAILED: 11/06/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/600,027	TANABE ET AL.	
	Examiner	Art Unit	
	Konstantina Katcheves	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4,6,9 and 10* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4,6,9 and 10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *detailed action* .

DETAILED ACTION

Claims 1, 4, 6, 9 and 10 are pending in the instant application. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Response to Amendment

The rejections of claims 2, 3, 5, 7, 8 and 11-13 are moot in light of the cancellation of these claims in Applicant's Amendment filed 30 August 2001.

Claims 9 and 10 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for the reasons of record in Official Action mailed 27 February 2001 and further discussed below.

Claims 1, 9, and 10 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for using a mutator gene (a gene defective in mismatch repair) for the method, does not reasonably provide enablement for any other means of introducing more mutations into one genomic DNA strand than another. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims for the reasons of record in Official Action mailed 27 February 2001 and further discussed below.

The rejection of claims 1-13 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for introducing many more point mutations into one

strand of double-stranded genomic DNA of a cell in which strand-specific differences in replication fidelity and mutators have been characterized, does not reasonably provide enablement for this mutagenesis method in other organisms has been withdrawn in view of Applicant's Amendment filed 30 August 2001.

The rejection of claims 1-4, 9, and 10 under 35 U.S.C. 102(b) as being anticipated by Fijalkowska et al. (1998. Proc. Natl. Acad. Sci. USA 95:10020-10025) has been withdrawn in view of Applicant's Amendment filed 30 August 2001.

The rejection of claims 1-4 and 9 under 35 U.S.C. 102(b) as being anticipated by Lin et al. (U.S. Patent 5,348,872) has been withdrawn in view of Applicant's Amendment filed 30 August 2001.

The rejection of claims 9 and 10 are rejected under 35 U.S.C. 102(b) as being anticipated by Pan et al. (1996. Antimicrobial Agents and Chemotherapy 40:2321-2326) has been withdrawn in view of Applicant's Amendment filed 27 August 2001.

The rejection of claims 9 and 10 under 35 U.S.C. 102(b) as being anticipated by Garza et al. (1995. Proc. Natl. Acad. Sci. USA 92:1970) has been withdrawn in view of Applicant's Amendment filed 30 August 2001.

The rejection of claims 9 and 10 under 35 U.S.C. 102(b) as being anticipated by Herbst et al. (1994. Proc. Natl. Acad. Sci. USA 91:12525-12529) has been withdrawn in view of Applicant's Amendment filed 30 August 2001.

The rejection of claims 9 and 10 under 35 U.S.C. 102(b) as being anticipated by Ota et al. (1992. Proc. Natl. Acad. Sci. USA 89:2355-2359) has been withdrawn in view of Applicant's Amendment filed 30 August 2001.

The rejection of claims 9 and 10 under 35 U.S.C. 102(b) as being anticipated by Sussel et al. (1991. Proc. Natl. Acad. Sci. USA 88:7749-7753) has been withdrawn in light of Applicant's Amendment filed 30 August 2001.

The rejection of claims 1, 4, 6 and 9 under 35 U.S.C. 103(a) as being unpatentable over Fijalkowska et al. in view of Lin et al. and further in view of either Imamoto et al. (U.S. Patent 5,928,866), or, alternatively, Iwaki et al. (1996. Mol. Gen. Genet. 251:657-664) have been withdrawn in light of Applicant's Amendment filed 30 August 2001.

Claims 1, 4, 6, 9 and 10 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Fijalkowska et al. and Lin et al., in view of either Imamoto et al. or Iwaki et al. and further in view of Pan et al. (1996 Antimicrobial Agents and Chemotherapy 40:2321-2326).

Response to Arguments

Claims 9 and 10 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant has failed to present arguments in response to the rejection of record in the Amendment filed 30 August 2001. Absent any traversal, claims 9 and 10 remain rejected for the reasons of record.

Claims 1, 9, and 10 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for using a mutator gene (a gene defective in mismatch repair) for the method, does not reasonably provide enablement for any other

means of introducing more mutations into one genomic DNA strand than another. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Applicant argues that the method of the present invention is "not a conventional method" because it "randomly introduces mutations into genomic DNA and selects cells or organisms having tolerance to a given [stress] condition." This argument is noted, however, does not overcome the instant rejection. The claims as written are broadly drawn to a method encompassing mutagenizing one strand preferentially in ways that do not involve the use of mutators in mismatch-repair, and encompassing such mutagenesis in any organism. The claims are not specifically drawn to a method for introducing mutations into genomic DNA and further to selecting organisms having tolerance to a stress condition. Furthermore, Applicant has failed to provide arguments or evidence overcoming the state of the art and the unpredictability of the art made of record in Official Action mailed 27 February 2001.

The prior art teaches that mutations occur during DNA replication, and teaches that these mutations occur preferentially in one strand (see for example Iwaki et al. 1996. Mol. Gen. Genet. 251:657-664, and Fijalkowska et al. 1998. Proc. Natl. Acad. Sci. USA 95:10020-10025). Thus, when there is a mutation in a DNA polymerase subunit that increases the mutation rate based on deficient proofreading activity during replication, or a mutation in a gene involved in mismatch repair such that errors from replication are not repaired, the increased number of mutations will occur more in one strand than another. However, the Examiner has not found in the art a teaching of another means, aside from

the use of mutator genes, of obtaining more mutations in one strand than the other. Thus, it is unpredictable how one would achieve such mutagenesis without the use of mismatch-repair mutators. The specification and working examples are limited to mutagenesis with the temperature-sensitive mutator *dnaQ49*. There is no guidance as to how to effect more mutations in one strand than another in a way that does not use mutator genes that are defective in mismatch repair.

Claims 1, 4, 6, 9 and 10 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Fijalkowska et al. and Lin et al., in view of either Imamoto et al. or Iwaki et al. and further in view of Pan et al. (1996 Antimicrobial Agents and Chemotherapy 40:2321-2326) for the reasons of record in Official Action mailed 27 February 2001 and further discussed below.

In traverse of the instant rejection, Applicant asserts that Pan et al. did not repeat the step of introduction of mutation under a certain condition and the step of selection of mutant under a selection condition and that the subsequent mutations are carried out under the same selection condition. Applicant's argument has been noted, yet is not persuasive.

Applicant's claims as amended are broadly drawn to a method encompassing mutagenizing one strand preferentially in ways that do not involve the use of mutators in mismatch-repair. Furthermore, the invention is broadly drawn to a method wherein multiple mutations of genomic DNA are accomplished under the same selection conditions.

Contrary to Applicant's argument, Pan teaches selection of ciprofloxacin-resistant

mutants of *Streptococcus pneumoniae* with mutation in genomic DNA that were generated by stepwise selection at increasing drug concentrations. Pan teaches that some mutants were isolated and selected with the same selection load, i.e. drug concentration, as the previously selected mutants (see page 2322, right column, and page 2323). This method is consistent with the steps of Applicant's claims wherein the same condition is provided for the subsequent steps in the method.

Applicant also argues that, "although the antibiotic is not the same, the tolerance rate of the mutant of this invention is much superior to that of Pan." The comparison made by Applicant is not convincing nor appropriate. The cellular mechanisms of ciprofloxasin and ampicillin activity differ such that one cannot make the statement that the tolerance rate of a mutant cell to ampicillin is greater than a mutant cell to ciprofloxacin.

Therefore, for the reasons of record and the arguments above the instant claims remain rejected.

Rejection Necessitated by Applicant's Amendment

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 4, 6, 9 and 10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 has been amended to include further limitations. However, the amended fail to clearly claim Applicant's invention. Claim 1 recites the language "many more." However, the claim fails to provide a frame of reference or comparison from which the skilled artisan may quantify to what "many more" refers.

Claim 1 also recites the limitation "derived from." "Derived" is a term that is non-specific and relative in nature for which Applicant provides no definition. It provides no clarity as to what Applicant's claimed invention includes and what it does not include. Without a more specific definition of the claim, it is impossible to determine what and how many derivations comprise the invention. The nature and number of the derivations to arrive at the invention Applicant seeks to protect with the patent are not established such that a person skilled in the art may determine the metes and bounds of the claims.

Claim 1 recites the limitation "the second time." This limitation is vague and indefinite because the claim does not necessarily recite a "first time." Therefore, it is not clear after which mutation step one of skill in the art performs a mutation step for the "second time." Furthermore, the limitation "the second time" lacks antecedent basis in the claims.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Konstantina Katcheves whose telephone number is (703) 305-1999. The examiner can normally be reached on Monday through Friday 7:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, George Elliott can be reached on (703) 308-4003. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-3014 for regular communications and (703) 305-7939 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 305-3388.

Konstantina Katcheves
October 30, 2001

REMY YUCEL, PH.D
PRIMARY EXAMINER